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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,178	09/24/2003	Tadanori Mayumi	MAYUMI2A	4046

7590 06/02/2006

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EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,178	MAYUMI ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/354,985.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/24/03&10/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _.

DETAILED ACTION

RE: Mayumi et al.

1. The information disclosure statement (IDS) filed on 10/18/2005 has been considered. A signed copy is attached hereto.

The information disclosure statement filed 9/24/03 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered as it pertains to the foreign prior arts JP 4-46928, JP 62-45208 and JP 62-289522 which are in Japanese.

2. Claims 1-12 are pending and under examination.

Specification

3. The first line of the specification should be updated if applicant desires priority under 35 U.S.C. 1 19(e), 120, 121 and 3654c) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application (s) (whether patented or abandoned) should also be

included. If a parent application has become a patent, the expression "now Patent No.___" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

For additional information, see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 4, 8 and 12 are indefinite for reciting "derivatives" in claim 4 as the exact meaning of the word is not known. The term "derivative" is not one, which has a universally accepted meaning in the art nor is it one which has been adequately described in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase. Since it is unclear how the homopolymers and copolymers are to be derivatized to yield the class of molecules referred to in the claims, a person of skill in the art cannot ascribe a discrete and identifiable class of molecules to said phrase.

B. Claims 5-12 are indefinite for reciting "susceptive diseases" in claims 5-8 as the exact meaning of the term is not known. The term "susceptive diseases" is vague and indefinite because it is unclear what the diseases are susceptive to? Are they susceptive to environment? malnutrition? biochemical imbalance? Are these susceptive diseases related to TNF activity?

C. Claims 5-12 are indefinite for reciting "where Xaa is a member selected from the group consisting of asparagine, alanine, arginine, serine, threonine, proline, methionine and leucine in claims 2". It is unclear whether the six Xaa in SEQ ID NO.2 are all the same (i.e. one type of amino acid) or they can be different (i.e. combinations of the different amino acids).

D. Claims 1-12 are indefinite for reciting "a high molecular part" in claims 1-4. The meaning of "a high molecular part" is unclear. What is the high molecular part? Is it a protein or polyethylene glycol? Does the "high molecular" mean "high molecular weight"?

E. Claims 1-12 are indefinite for reciting "bound artificially" in claim 1. What is the natural way of binding? Is it covalent binding or a binding like between an antibody and an antigen?

F. Claims 1-12 are indefinite for reciting "TNF activity" in claim 1. The meaning of "TNF activity" is unclear. Is it a particular characteristic or a function of the protein that distinguishes one from another or is it a proinflammatory activity, or an anti-tumor or an anti-bacterial activity?

Claim Rejections - 35 USC § 112, 1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Due to indefinite nature of the claims (see paragraph 5 above), the "high molecular part" is interpreted here as "high molecular weight part".

Claim 1 recites "a proteinaceous part with TNF activity", and "a high molecular weight part". Claims 1-12 encompass any protein having TNF activity. The claims therefore encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property. The instant specification only describes a protein of SEQ ID NO.2, wherein Xaa is a member selected from the group consisting of asparagines, alanine, arginine, serine, threonine, praline, methionine, and leucine (see page 4, 2nd paragraph). There is insufficient written description regarding "a proteinaceous part with TNF activity" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a protein having TNF activity are not set forth in the specification as-filed, commensurate in scope with the claimed invention.

Moreover, the claims encompass a genus of molecules or material which have high molecular weight, such as DNA, protein, metal, etc. The instant specification only describes water-soluble polymers. Therefore, the written description is not commensurate in scope with the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-probe Inc.,* 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, "a proteinaceous part with TNF activity" does not distinguish any particular

protein with TNF activity from others having the same activity or function and as such does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406.

In the absence of structural characteristics that are shared by members of the genus of a "proteinaceous part with TNF activity", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of all "proteinaceous part with TNF activity". Moreover, applicant was not in possession of all "high molecular weight part". Applicant was only in possession of "water soluble polymer". See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Claim Rejections - 35 USC § 112, 1st paragraph

8. Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agent for treating tumor, does not reasonably provide enablement for treating any and all susceptive diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to an agent for susceptive diseases. The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass an agent for treating any susceptive diseases. The specification defines the “susceptive diseases” as any diseases which can be treated and/or prevented by the administration of the physiologically active complex with or without other medicaments, including tumor, viral diseases, bacterial diseases and immunopathies (see last paragraph on page 8 and lines 5-6, page 9).

Quantity of experimentation

The quantity of experimentation in this area is extremely large since applicants broadly claim treating any susceptive diseases using the claimed agent. It would

require significant study to identify which diseases including cancer, viral diseases, bacterial diseases and immunopathies can in fact be treated by the claimed agent. The identification and characterization of each of the diseases would be inventive, unpredictable, and difficult in itself, requiring years of inventive effort with no guarantee of success in doing so.

The state of the prior art and the predictability or lack thereof in the art:

Shin et al. teach that human TNF muteins wherein at least one of the 4th to the 10th, the 38th to the 41st, the 52nd to the 54th, the 56th, the 85th to the 88th, the 127th to the 129th, the 156th and the 157th amino acids of the wild type TNF polypeptide is replaced by another amino acid are capable of treating tumor (see page 2, lines 25-64, US Patent No. 5,773,582, issue date 6/30/1998). Terlikowski et al. teach TNF muteins which selectively bind to p55R receptor have antitumor activity (Terlikowski et al. Toxicology, 2002, 143-152). There is no teaching in the art that TNF muteins are capable of treating any other diseases.

Working examples:

The specification teaches that the physiological active complex comprising SEQ ID NO.2, wherein Xaa is a member selected from the group consisting of asparagines, alanine, arginine, serine, threonine, praline, methionine, and leucine, are effective in treating tumor (see examples 3 and 12), However, there in no data indicating that the claimed agent are also effective in treating other diseases.

Guidance in the specification

There is no data indicating that the claimed agent is capable of treating any diseases except tumor. The specification fails to provide any guidance on treating disease other than tumor using the claimed agent.

Level of skill in the art

The level of the skill in the art is deemed to be high

Conclusion:

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example on treating diseases other than tumor and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1, 3-5, 7-9 and 11-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Yu et al. ((U.S. Patent 6,541,224 B2, issued 04/01/2003, effective filing date at least 06/14/2001, IDS).

Due to indefinite nature of claims (see paragraph 4 above), claims 1, 3-5, 7-9 and 11-12 are interpreted as a physiologically active complex comprising a proteinaceous part conjugated to a high molecular weight part at the N-terminus of the proteinaceous part, wherein the proteinaceous part has TNF activity. Claims are further limited, wherein, the high molecular weight part has a molecular weight of 500-50,000 daltons, is selected from the group consisting of homopolymers of polyethylene glycol, and the said complex is an anti-tumor agent.

Yu et al teach a protein complex having anti-tumor activity, comprising a TNF protein coupled at the N-terminus of the TNF to a water-soluble polymer such as copolymers of polyethylene glycol having molecular weight between 1-100kDa (column 66, lines 13-27, column 67, lines 15-35, and column 158). Yu et al. teach that coupling TNF to polymers such as copolymers of polyethylene glycol increases solubility, stability, and decrease immunogenicity of the TNF (see column 66, lines 8-20).

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Hong Sang
Art Unit 1643
May 2, 2006